



## Secondary causes of diabetes: a crossroad of endocrinology and oncology

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Cancer and diabetes share a bidirectional relationship, with cancer increasingly recognised as an associated factor of diabetes, both from the disease itself and its treatments. In this Review, we aim to: (1) summarise the distinct mechanisms of dysglycaemia arising from cancer and neuroendocrine tumour treatments, including targeted therapies such as PI3K–AKT–mTOR inhibitors, antibody–drug conjugates, immune checkpoint inhibitors, corticosteroids, and somatostatin receptor ligands; (2) examine the often overlooked aspect of the secondary cause of diabetes as an early manifestation of cancer; and (3) highlight research gaps and encourage a collaborative care approach to manage the rising rate of dysglycaemia as a result of cancer and its evolving treatments. To address the first two objectives, we incorporate relevant case vignettes to contextualise the discussions.

### Introduction

Diabetes encompasses autoimmune type 1 with severe insulin deficiency, non-autoimmune type 2 with relative insulin deficiency, gestational diabetes, and other specific forms.<sup>1</sup> Although treatment pathways for type 1, type 2, and gestational diabetes are well established, the management of other forms of diabetes is less clearly defined. Understanding the pathways to dysglycaemia allows for accurate treatment. Glucose regulation is a complex process, which can involve irregular functioning of pancreatic islets and the target tissues (ie, liver, muscle, and fat), disruption of post-insulin signalling pathways, and actions of counter-regulatory hormones such as catecholamines and glucagon.<sup>2</sup> Autoimmunity, genetic, lifestyle, and life course factors interact with these pathophysiological pathways, either directly or via treatment-related mechanisms, to shape individual susceptibility to glucose dysregulation.<sup>2,3</sup>

In parallel with the rise of global incidence of diabetes and obesity, cancer incidence is projected to reach 35 million by 2050, a 77% increase from 2022.<sup>4</sup> Cancer and diabetes have common risk factors, with overweight and obesity being major underlying contributors to both conditions.<sup>5</sup> In addition, cancer and diabetes are closely intertwined and show a bidirectional relationship. Diabetes confers an increased risk of several cancers, especially for malignancies of the breast, gallbladder, colorectum, and endometrium.<sup>6</sup> Conversely, pancreatic cancer and some functional neuroendocrine tumours (NETs) can precipitate secondary diabetes.<sup>7–9</sup> In addition, treatments for these neoplasms can themselves induce new-onset diabetes.<sup>10</sup>

In this Review, we outline the mechanisms underlying secondary diabetes in people living with cancer, whether arising from cancer treatments or as a direct manifestation of the cancer itself. We use case vignettes to illustrate these pathways and conclude with future perspectives for clinical management and research.

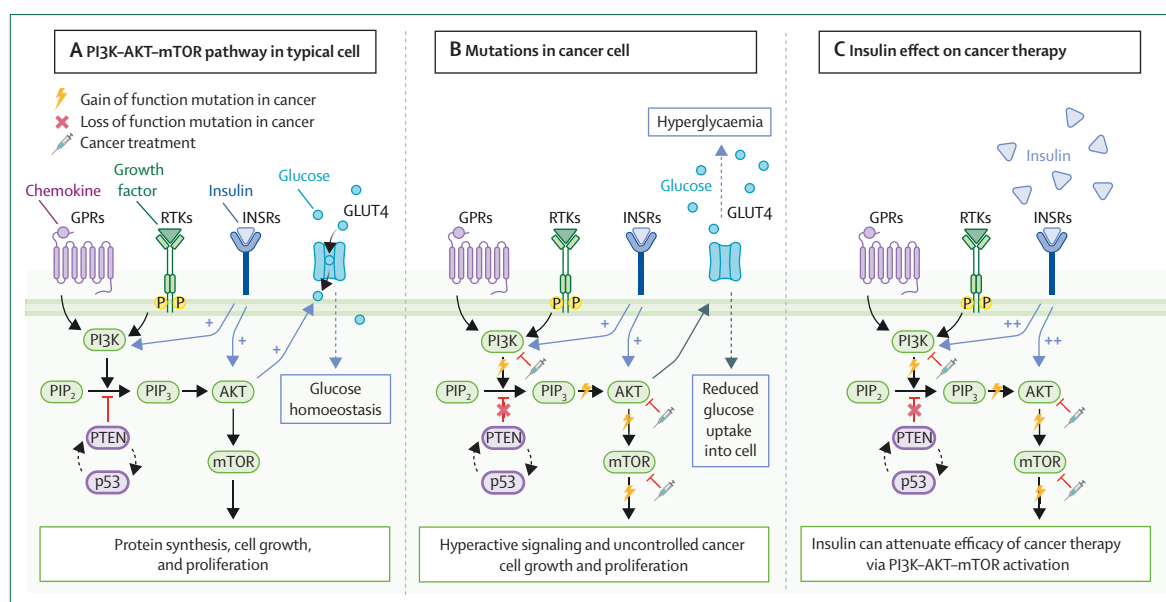
### Cancer treatment-related hyperglycaemia

Hyperglycaemia from cancer treatment can occur as an adverse drug effect, with severity ranging from mild and

reversible hyperglycaemia to severe disturbances that can result in permanent diabetes. A classic example of cancer treatment-induced diabetes is streptozocin. First approved in the 1980s for pancreatic NETs, this nitrosourea cytotoxic agent is selectively taken up by pancreatic  $\beta$  cells via glucose transporter 2 (GLUT2), conferring anti-tumour activity while inducing  $\beta$ -cell destruction, insulin deficiency, and thus, diabetes.<sup>11</sup> Streptozocin has been superseded by newer treatment modalities for pancreatic cancer, and other anti-cancer drug classes (as outlined in the following sections) are likewise increasingly associated with hyperglycaemia.<sup>12</sup>

### PI3K–AKT–mTOR pathway inhibitor-induced hyperglycaemia

The class I PI3K–AKT–mTOR signalling pathway regulates multiple cellular processes, including metabolism, apoptosis, and cell proliferation.<sup>13</sup> Dysregulations of this pathway have been observed in many malignancies, including pancreatic cancer,<sup>14</sup> breast cancer,<sup>15</sup> renal cell cancers,<sup>16</sup> and leukaemia.<sup>17</sup> Alterations commonly involve the loss of PTEN or activating mutations in *PIK3CA* and *AKT1*.<sup>14</sup> In normal physiology, the PI3K–AKT–mTOR pathway supports two principal functions: promoting cellular proliferation and regulating glucose metabolism (figure 1).<sup>16</sup> In typical circumstances, PTEN negatively regulates the PI3K–AKT–mTOR pathway, preventing replication if a mutation occurs, hence preventing replication of mutated cells. However when a cancer mutation specifically affects PTEN, the pathway becomes activated without any oncogenic stimulus, driving pathological cellular replication. The overactivation of AKT by PTEN is the most important carcinogenic factor in PTEN-deficient cancers.<sup>18</sup> Thus, AKT inhibitors used in cancer treatment inhibit the PI3K–AKT pathway, with reduced peripheral glucose uptake, and induce insulin resistance and hyperglycaemia. Insulin also activates the PI3K–AKT signalling pathway and promotes glucose uptake into adipose tissue and skeletal muscle by translocating GLUT4 to the cell surface.<sup>19</sup>



**Figure 1: The PI3K-AKT-mTOR pathway and dysglycaemia**

Created in BioRender. Ooi, Y. (2025) <https://BioRender.com/2yspkx0>. (A) The PI3K-AKT-mTOR pathway in a typical cell. Growth factors stimulate surface receptors, such as GPRs and RTKs, to regulate cell growth. INSR is an example of an RTK. Activation of these surface receptors recruits PI3K to the membrane, which triggers the PI3K-AKT-mTOR pathway, resulting in cellular proliferation. The PTEN and p53 proteins act as inhibitors for this pathway in response to various stimuli, including DNA damage response. Insulin also activates the PI3K-AKT signalling pathway, which promotes glucose uptake into cells by translocating GLUT4 to the cell surface. (B) The PI3K-AKT-mTOR pathway in a cancer cell. Mutations at any stage in the PI3K-AKT-mTOR pathway have the potential to increase the activity of some proteins or cause gain of function, setting off uncontrollable cellular proliferation. Similarly, mutations in the genes coding for PTEN and p53 result in the loss of function of these proteins to suppress the dysregulated proliferation of cancer cells. Cancer treatment targets various stages of this pathway to suppress this dysregulated proliferation. For example, PI3K-AKT-mTOR inhibitors reduce translocation of GLUT4 and peripheral glucose uptake, resulting in insulin resistance and hyperglycaemia. (C) Administration of exogenous insulin or insulin secretagogues can cause increased activity of the PI3K-AKT-mTOR pathway, potentially undoing the benefit of PI3K-AKT-mTOR inhibitors. GPR=G-protein-coupled receptors. INSR=insulin receptor. PIP<sub>2</sub>=phosphatidylinositol 4,5-bisphosphate. PIP<sub>3</sub>=phosphatidylinositol 3,4,5-trisphosphate. RTK=receptor tyrosine kinase.

Many anti-cancer treatments have been developed to target this pathway. Current treatments include isoform-specific and pan-PI3K inhibitors, dual PI3K-mTOR inhibitors, AKT inhibitors, mTOR inhibitors, allosteric mTOR inhibitors, ATP-competitive mTOR inhibitors, bistic mTOR inhibitors, and 3-phosphoinositide-dependent protein kinase-1 (PDK-1) inhibitors.<sup>20</sup> mTOR inhibitors, which have been used clinically longer than PI3K or AKT inhibitors, have a reported incidence of hyperglycaemia ranging from 12% to 50% for all grade events and 4% to 22% for grade 3-4 events (ie, grade 3: 13.9-27.8 mmol/L or admission to hospital indicated and grade 4:  $\geq 27.8$  mmol/L or life-threatening consequences).<sup>21</sup> Among PI3K inhibitors, hyperglycaemia is largely restricted to  $\alpha$ -isoform and pan-PI3K inhibitors, whereas  $\beta$ ,  $\delta$ , and  $\gamma$ -isoform PI3K inhibitors are not implicated, reflecting the central role of PI3K $\alpha$  in insulin signalling in adipocytes and myotubes.<sup>22,23</sup> Alpelisib and inavolisib (PI3K $\alpha$  inhibitors), capivasertib (AKT inhibitor), and temsirolimus, everolimus, and nab-sirolimus (mTOR inhibitors) are US Food and Drug Administration (FDA)-approved, whereas copanlisib, a pan-PI3K inhibitor, lost its accelerated approval in 2023 as it was unable to show clinical benefit in further studies.<sup>24,25</sup> In randomised trials, the incidence of all-grade

hyperglycaemia was 63.7% for alpelisib,<sup>26</sup> 58.6% for inavolisib,<sup>27</sup> 16.3% for capivasertib,<sup>28</sup> 22.0% for temsirolimus,<sup>29</sup> and 13.2% for everolimus.<sup>30</sup> Nab-sirolimus showed an incidence of 41.2% in a phase 2 study.<sup>31</sup> The PI3K $\alpha$  inhibitor alpelisib and the AKT inhibitor capivasertib are the most frequently used in clinical practice, although their adoption is limited by cost in many settings.

PI3K-AKT-mTOR pathway inhibitor-induced hyperglycaemia can be severe and clinically significant. In a single centre retrospective study of 491 people treated with PI3K or AKT inhibitors, hyperglycaemia requiring treatment disruption, dose interruption, or dose reduction occurred in 5% of individuals on AKT inhibitors, 13% of individuals on PI3K $\alpha$  inhibitors, and 5% of individuals on pan-PI3K inhibitors.<sup>22</sup> Pharmacovigilance analysis reported an odds ratio of 9.84 (95% CI 7.3-13.2) for diabetic ketoacidosis episodes, including admission to hospital and death, with PI3K $\alpha$  inhibitors (such as alpelisib), which had a ten times higher risk than all other anti-cancer treatments.<sup>32</sup>

Although several studies of PI3K-AKT-mTOR inhibitors suggested that an age of less than 65 years, a history of diabetes, and administration of AKT and dual PI3K-mTOR inhibitors were risk factors for

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hyperglycaemia in various cancers,<sup>33</sup> these findings have not been consistently reproduced. Reports on PI3K $\alpha$  inhibitors, such as alpelisib, indicate that elevated baseline HbA<sub>1c</sub> and BMI, a history of gestational diabetes, and Asian ethnicity might confer increased risk.<sup>22,34,35</sup> Whether these associations reflect drug-specific effects or a broader class effect has yet to be established.

A distinctive feature of hyperglycaemia induced by PI3K–AKT–mTOR inhibitors is its reversibility. Dose reduction or temporary interruption typically leads to rapid normalisation of hyperglycaemia,<sup>34–36</sup> unlike the persistent hyperglycaemia seen in type 2 diabetes or checkpoint inhibitor-associated autoimmune diabetes (CIADM; outlined in the following section). However, dose adjustment decisions are often made in the context of balancing metabolic adverse effects against the imperative to preserve anti-cancer efficacy, particularly given the availability of effective glucose-lowering treatments.<sup>37</sup> The landmark SOLAR-1 trial with alpelisib had a protocol amendment midway through the trial to improve the detection and management of hyperglycaemia, with the aim of actively preventing dose adjustments and discontinuations of alpelisib.<sup>38</sup>

Given the scarcity of randomised trials in this field, expert Delphi consensus recommendations have outlined strategies for monitoring and managing PI3K $\alpha$  inhibitor-induced hyperglycaemia.<sup>34</sup> Metformin is widely used as first-line treatment for PI3K–AKT–mTOR inhibitor-induced diabetes.<sup>22,34,37</sup> Its mechanisms (amelioration of insulin resistance and suppression of hepatic gluconeogenesis) directly counteract the hyperglycaemic effects of PI3K–AKT–mTOR inhibitors and underpin its use in landmark trials, such as SOLAR-1 with alpelisib.<sup>26</sup> Due to the high incidence of hyperglycaemia, the consensus also proposed prophylactic metformin in people with prediabetes and normoglycaemia treated with these agents. In an open-label phase 2 trial, in which metformin was initiated alongside alpelisib, grade 3–4 hyperglycaemia occurred in only 2·1% (1/48) of participants with normoglycaemia and in 15·0% (3/20) of those with prediabetes.<sup>39</sup> This approach is not without potential concerns as metformin activates AMPK, a pathway influenced by PI3K inhibition, and uncertain implications for anti-cancer efficacy.<sup>37,40</sup>

Non-insulin-mediated glucose-lowering strategies, including SGLT2 inhibitors, have been proposed.<sup>34,35,37</sup> However, SGLT2 inhibitors require caution, as several cases of diabetic ketoacidosis occurred during their use, with the incidence rate of diabetic ketoacidosis estimated to be 48 cases per 100 patient-years (95% CI 6–171) for alpelisib plus SGLT2 inhibitor and five cases per 100 patient-years (95% CI 2–53) for alpelisib plus non-SGLT2 inhibitor glucose-lowering treatments.<sup>36,41,42</sup> Other glucose-lowering treatments, such as thiazolidinediones, GLP-1 receptor agonists, and dipeptidyl peptidase-4 (DPP4) inhibitors, appear to have

low effectiveness in the context of PI3K inhibition in,<sup>22</sup> and are generally considered to be second-line or third-line options.<sup>34,37</sup>

The use of sulfonylureas and exogenous insulin in PI3K–AKT–mTOR inhibitor-induced hyperglycaemia remains controversial. Animal models suggest that hyperinsulinaemia can reactivate the PI3K–mTOR signalling pathway in tumour cells, compromising the anti-cancer efficacy.<sup>43</sup> Hence, sulfonylureas and insulin are generally reserved for situations in which other glucose-lowering treatments are ineffective, or for the management of diabetic ketoacidosis and other diabetic emergencies.<sup>34,37,44</sup> The consensus statement on PI3K $\alpha$  inhibitors recommends initiating insulin only when non-insulin glucose-lowering treatment has been maximised for patients, and the glucose concentration is above 13·9 mmol/L (250 mg/dL) after consultation with endocrinologists.<sup>34</sup> Another Review deviated from this consensus and advised ketone and C-peptide measurements at first recognition of hyperglycaemia.<sup>45</sup> Nevertheless, both recommendations concur that insulin should be used as a rescue therapy only after maximising non-insulin treatments.<sup>34,45</sup>

Although several studies recommend dose reduction or temporary withdrawal of PI3K–AKT–mTOR inhibitors when hyperglycaemia cannot be controlled with glucose-lowering treatments,<sup>20,34</sup> definitions of the thresholds for targeted therapy de-escalation vary. The consensus statement on PI3K $\alpha$  inhibitors advises withholding treatment when the plasma glucose concentration exceeds more than 13·9 mmol/L (250 mg/dL), and considering permanent discontinuation if the plasma glucose concentration rises to more than 27·8 mmol/L (500 mg/dL) despite maximising non-insulin treatments.<sup>34</sup> Panel 1 describes a case vignette of a person who developed new-onset diabetes and presented with diabetic ketoacidosis shortly after initiating the AKT inhibitor capivasertib.

### Antibody–drug conjugates

Antibody–drug conjugates are an emerging class of targeted anti-cancer treatments consisting of a monoclonal antibody directed against tumour-associated antigens, a cleavable linker, and a potent cytotoxic payload.<sup>46</sup> Upon antigen binding, the antibody–drug conjugate–antigen complex is internalised, and the linker is cleaved within lysosomes, releasing the payload to induce cell death.<sup>46</sup> Within this class, enfortumab vedotin, approved for advanced urothelial carcinoma, is increasingly reported to precipitate clinically significant hyperglycaemia.<sup>47</sup> The mechanism is not fully understood, but is thought to involve cytotoxic stress from metabolic effects of the payload, potentially worsening insulin resistance.<sup>48</sup> Meta-analyses of clinical trials reported an overall hyperglycaemia incidence of 10·3% (95% CI 8·6–12·2), with an elevated relative risk of 16·97 (95% CI 6·22–48·25).<sup>49</sup> Real-world data reported

a lower incidence (3.3%),<sup>50</sup> although three cases of diabetic ketoacidosis have been reported.<sup>48</sup> Similar severe hyperglycaemia and diabetic ketoacidosis events have been reported with brentuximab vedotin, used in lymphoma, but overall incidence remains unclear.<sup>51–54</sup> As enfortumab vedotin is often co-administered with pembrolizumab, and brentuximab vedotin with nivolumab, the possibility of CIADM should also be considered.

### Checkpoint inhibitor-associated autoimmune diabetes

Immune checkpoint inhibitors (ICIs) have transformed oncology care since their US FDA approval in 2011.<sup>55</sup> Their use has expanded rapidly, and they are now an essential cancer therapy, benefiting half of all people with metastatic cancer.<sup>56</sup> Current ICI classes largely consist of monoclonal antibodies targeting cytotoxic T-lymphocyte associated antigen 4 (CTLA4), programmed cell death protein 1 (PDCD1), and programmed cell death 1 ligand 1 (PD1L1) receptors. Both CTLA4 and PDCD1 are expressed on T cells, whereas PD1L1 is expressed on pancreatic  $\beta$  cells.<sup>57</sup> Stimulation of these receptors suppresses T-cell activation, induces immune tolerance, and prevents autoimmunity.<sup>57</sup> However, cancer cells can exploit these pathways to develop an immunosuppressive microenvironment that promotes tumour growth.<sup>57</sup> Pharmacological inhibition of these immunomodulating receptors restores anti-tumour immunity and improves cancer control, but this increased immune activation can precipitate immunorelated adverse events, including autoimmune diabetes and other endocrinopathies.

The term CIADM was coined to describe a distinct form of autoimmune diabetes.<sup>58</sup> Although ICIs often induce immunorelated endocrinopathies, CIADM is comparatively uncommon. Incidence rates differ by therapeutic target and by generation of ICI.<sup>59</sup> Earlier ICIs, such as the PDCD1 inhibitor pembrolizumab and the PD1L1 inhibitor atezolizumab, have been associated with CIADM incidences of 0.4% and 1.4%, respectively.<sup>60</sup> By contrast, higher incidences of hyperglycaemia have been shown for newer ICIs, including for the PDCD-1 inhibitor camrelizumab (4.8%) and for the PD1L1 inhibitor durvalumab (1.8%).<sup>59</sup> The risk of endocrine toxicity further increases with combination treatments.<sup>60</sup> Although CIADM is exceedingly rare in CTLA4 inhibition alone, the combination of durvalumab and the CTLA4 inhibitor tremelimumab increased the hyperglycaemia incidence to 3.1% compared with 1.8% for PD1L1 monotherapy.<sup>59</sup>

A 2023 systematic review of 192 people meeting the diagnostic criteria for CIADM, defined by hyperglycaemia (blood glucose concentration >11 mmol/L or HbA<sub>1c</sub>  $\geq$ 6.5% [47.5 mmol/mol]) alongside insulin deficiency (C-peptide concentration <0.4 nmol/L or presentation with diabetic ketoacidosis), reported that 69.7% of people presented with diabetic ketoacidosis at diagnosis, with a median onset of

### Panel 1: Case vignette of AKT inhibitor-induced diabetic ketoacidosis

#### Patient demographics and presentation

A 57-year-old woman with a history of metastatic breast cancer, but no pre-existing type 2 diabetes, was admitted to the hospital with a diagnosis of diabetic ketoacidosis 10 months after being initiated on capivasertib, a pan-AKT inhibitor, and palbociclib, a CDK4 and CDK6 inhibitor.

#### Medical history and treatment context

She was first diagnosed with cancer of the left breast in 1999, followed by cancer of the right breast in 2013. She underwent sequential mastectomy with axillary clearance both times, followed by adjuvant chemotherapy and radiotherapy bilaterally. The tumour was positive for oestrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2, also known as ERBB2).

In March, 2024, she was found to have right lung, liver, and bone metastases, as well as left axillary and abdominal nodal involvement. A biopsy of the lung mass revealed that the tumour was positive for oestrogen receptor and progesterone receptor, but negative for HER2. She was started on capivasertib and palbociclib as part of a clinical trial.

#### Adverse events and onset of dysglycaemia

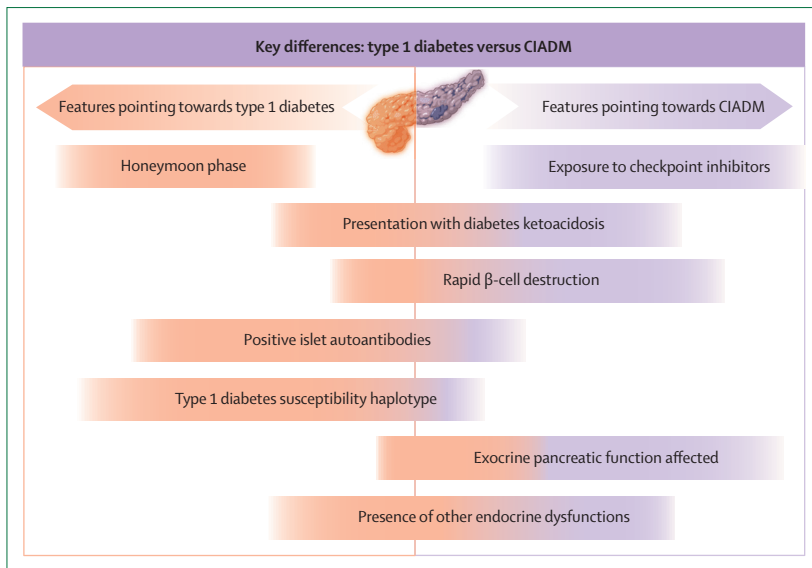
During treatment with capivasertib and palbociclib, she had multiple adverse events that were not glycaemia-related, including skin rashes, oral mucositis, and lung empyema. These adverse events required withholding capivasertib intermittently. Dose reduction was done due to the occurrence of these adverse events.

Glycaemic status was monitored with HbA<sub>1c</sub>. In June, 2024, before the initiation of capivasertib and palbociclib, she had an HbA<sub>1c</sub> of 5.6% (38 mmol/mol). In September, 2024, she had an HbA<sub>1c</sub> of 5.8% (40 mmol/mol), in the context of a declining blood haemoglobin concentration from 141 g/L to 106 g/L, which might have resulted in a falsely low HbA<sub>1c</sub>. In December, 2024, her HbA<sub>1c</sub> was 6.6% (49 mmol/mol; haemoglobin 127 g/L). Capivasertib dose reduction, fasting glucose, haemoglobin, and other adverse events over the course of her treatment are summarised in the appendix (p 2). She was admitted in April, 2025, with a 2-day history of reduced effort tolerance, loose stools, and nausea. She stated that she had no weight loss, polyuria, or polydipsia. Her BMI was 17.1 kg/m<sup>2</sup>. Her venous blood glucose concentration was 23.8 mmol/L, pH was 7.28, bicarbonate concentration was 15.9 mmol/L, and serum ketone concentration was 3.3 mmol/L. She was diagnosed with diabetic ketoacidosis and treated with insulin infusion and intravenous fluids. Her diabetic ketoacidosis resolved within 6 h. The insulin infusion was stopped after 12 h once the patient was able to take food and fluids orally. Due to this severe adverse event, the oncologist discontinued capivasertib, after which glucose concentration improved to 4.3–6.1 mmol/L during her hospital stay, without the need for insulin.

1 month after recovery from diabetic ketoacidosis and capivasertib cessation, comprehensive assessment of insulin reserve and resistance showed normal results (homeostatic model assessment of insulin resistance: 0.29 [normal  $\leq$ 1.6, liver insulin resistance:  $\geq$ 2.5]; Matsuda index: 9.01 [whole body insulin resistance  $\leq$ 2.5], insulinogenic index: 0.67 [insulin secretory defect <0.4]; disposition index: 6.07 [normal >1]), and islet and insulin autoantibodies (GAD, anti-IA-2A, and anti-IAA) were negative. 2 months after capivasertib cessation, HbA<sub>1c</sub> was 5.2% (33.3 mmol/mol) in June, 2025, without any glucose-lowering therapy. She has since been treated with palbociclib and fulvestrant for metastatic breast cancer.

#### Learning points

AKT inhibitors and other PI3K-AKT-mTOR inhibitors induce insulin resistance, leading to hyperglycaemia that is typically reversible upon treatment interruption. In some cases, hyperglycaemia can progress to diabetic ketoacidosis. Although HbA<sub>1c</sub> is often used to screen for diabetes, it can be misleadingly normal in patients with anaemia or acute-onset diabetes. Hence, plasma glucose or capillary blood glucose should be monitored either in the clinic or at home, with monitoring frequencies consistent with existing recommendations.



**Figure 2: Overlaps between characteristics of type 1 diabetes and CIADM**

Created in BioRender. Ooi, Y. (2025) <https://BioRender.com/1m57pqj>. Overlap between the characteristics of type 1 diabetes (orange colour) and CIADM (purple colour). Type 1 diabetes has more antibody positivity and has a higher prevalence of type 1 diabetes haplotypes. CIADM presents with more diabetic ketoacidosis, has a higher prevalence of  $\beta$ -cell destruction, more exocrine pancreas involvement as evidenced by high lactase concentrations, and has a higher prevalence of coexisting endocrine disorders due to immune checkpoint inhibitors. The honeymoon phase is exclusive to type 1 diabetes, and exposure to immune checkpoint inhibitors is exclusive to CIADM. The degree of overlap is a graphical estimate and is not meant to represent absolute values between conditions. CIADM=checkpoint inhibitor-associated autoimmune diabetes.

See Online for appendix 11.7 weeks (IQR 6–24) after ICI initiation.<sup>58</sup> This finding underscores the importance of systematic surveillance and early recognition of this potentially fatal complication. ICI use has also been shown to worsen dysglycaemia in people with pre-existing type 2 diabetes. One study showed that 55% of people with type 2 diabetes developed hyperglycaemia after ICI use, postulated to be due to a combination of factors, including but not limited to, co-administration of steroids and indirect consequences of other immune-related complications.<sup>61,62</sup> Notably, 91.6% of people with CIADM had particularly low concentrations of plasma C-peptide (<0.4 nmol/L) at the onset of hyperglycaemia, a feature that differentiates CIADM from type 2 diabetes in adults.<sup>58</sup>

Although the treatment of CIADM broadly mirrors that of type 1 diabetes, several key differences distinguish the two conditions (figure 2). CIADM is characterised by a rapid loss of  $\beta$ -cell function, with almost complete absence of insulin-producing cells.<sup>63</sup> Hence, in contrast to autoimmune type 1 diabetes with some residual islet function, a honeymoon phase is typically absent in people with CIADM.<sup>64</sup> Islet autoantibodies are also less prevalent in CIADM than in type 1 diabetes (0–71% vs 90%).<sup>64</sup> When present, GADA is the most prevalent (39.7%), followed by IA-2A (13.9%), IAA (8.9%), ICA (6.0%), and ZNT8 (2.9%).<sup>58</sup> People with positive insulin autoantibodies have an earlier onset of CIADM by 3.5 weeks, irrespective of ICI used.<sup>58</sup> CIADM also has

more exocrine pancreatic involvement,<sup>64</sup> with up to 69.4% of patients showing elevated lipase.<sup>58</sup>

As with type 1 diabetes, once CIADM develops, it requires lifelong insulin therapy.<sup>64</sup> Unlike PI3K–AKT–mTOR inhibitors, ICI withdrawal does not reverse diabetes. Given that CIADM follows a rapid and fulminant course, strategies for glucose monitoring are needed for early detection and treatment. A multidisciplinary consensus has proposed a tiered risk-stratification approach to guide monitoring.<sup>65</sup> People with pre-existing type 2 diabetes, a baseline glucose concentration of more than 11.1 mmol/L (200 mg/dL), or an HbA<sub>1c</sub> of 6.5% (48 mmol/mol) or more are at high risk of hyperglycaemia with ICI therapy.<sup>65</sup> This high-risk group should be equipped with glucometers and educated on self-monitoring of blood glucose. People at moderate risk, defined as those without known diabetes, but with baseline lipase elevation or concomitant glucocorticoids, should undergo glucose monitoring every two weeks, together with fingerstick testing at clinic visits. People at low risk should receive quarterly assessment with HbA<sub>1c</sub> and fasting plasma glucose (FPG) concentrations.<sup>65</sup>

Although no formal international guideline exists for glucose monitoring during ICI treatment, baseline assessment with HbA<sub>1c</sub> and a 75 g oral glucose tolerance test can help identify pre-existing dysglycaemia before treatment initiation.<sup>66</sup> Regular self-monitoring of blood glucose, particularly during the first 3 months of ICI treatment when the risk of CIADM onset is the highest, is advisable. Given the substantial proportion of people who present with diabetic ketoacidosis at initial diagnosis, education on the symptoms of this condition is essential. Panel 2 describes a case vignette of a person with pre-existing type 2 diabetes who had worsening hyperglycaemia during ICI treatment.

### Corticosteroid-induced diabetes

Corticosteroids have been used in cancer care since the 1950s, initially for haematological malignancies. Their role has since broadened to encompass multiple facets of cancer care, including direct cytotoxicity,<sup>67–72</sup> anti-inflammatory,<sup>73,74</sup> management of immunotherapy-related adverse events,<sup>69,75</sup> and pre-medication for hypersensitivity prevention,<sup>76</sup> anti-emesis,<sup>77</sup> appetite stimulation,<sup>78</sup> and symptom palliation in advanced cancer.<sup>79</sup> Reflecting their pleiotropic effects, dosing and treatment regimens differ by indication, but often require high doses of potent corticosteroids, making adverse effects not uncommon. The table summarises the principal indications, mechanisms of action, and commonly used corticosteroid regimens in oncology.

Corticosteroid-induced diabetes refers to new-onset hyperglycaemia that fulfils standard diagnostic criteria for diabetes in people without pre-existing diabetes after the initiation of corticosteroids. It is distinct from corticosteroid-induced hyperglycaemia, which reflects

worsening of glycaemic control in people with pre-existing diabetes. Its pathophysiology arises from complex hormonal crosstalk, mainly mediated by glucocorticoid receptor signalling. Key mechanisms include: (1) increased caloric intake due to central appetite stimulation via leptin resistance; (2) systemic insulin resistance in skeletal muscle, adipose tissue, and the liver, resulting in reduced peripheral glucose uptake and increased hepatic gluconeogenesis; (3) altered insulin receptors and consequently their binding capacity, causing insulin resistance and delayed hypoglycaemia; and (4) chronic exposure impairing insulin secretion due to  $\beta$ -cell apoptosis and the suppression of osteocalcin, a bone-derived endogenous insulin secretagogue.<sup>83–85</sup> The reported incidence of corticosteroid-induced diabetes in cancer treatment ranges from 9% to 40%, varying by patient cohort and corticosteroid regimen.<sup>86,87</sup> Risk factors can be broadly classified into patient-related and drug-related factors. Patient-related factors mirror those for type 2 diabetes and include advanced age, ethnic predisposition, overweight and obesity, previous glucose intolerance, a family history of diabetes, smoking, and comorbidities (eg, hypertension, hypertriglyceridemia, and impaired kidney function).<sup>88</sup> Age is the strongest of these risk factors.<sup>87</sup> Drug-related factors include corticosteroid potency, dose, schedule, and co-administration of medications, including diuretics and immunosuppressants. Hyperglycaemia risk increases with increasing treatment duration, with continuous regimens conferring greater risk than the cyclical regimens typically used in oncology.<sup>86</sup> The corticosteroid regimens commonly used in cancer care are summarised in the appendix (p 3).

Corticosteroid-induced hyperglycaemia typically emerges at pragmatic high-dose thresholds of 20 mg or more prednisolone-equivalent per day,<sup>89</sup> but risk is dependent on both dose and duration.<sup>90</sup> Hence, most guidelines recommend screening from doses as low as 5 mg or more prednisolone-equivalent per day.<sup>91</sup> Understanding the potency and pharmacokinetics of individual corticosteroids and the intrinsic patient risk for diabetes is crucial for appropriate screening, monitoring, and management.<sup>92</sup> Notably, anti-inflammatory potency might not equate the hyperglycaemic effect, and both the duration of action and glycaemic effects can extend beyond the plasma half-life. This protracted effect reflects glucocorticoid receptor-mediated transcriptional activation, for which downstream protein responses persist long after plasma clearance.<sup>92</sup>

Following corticosteroid initiation, diabetes can develop within the first week in people at risk, whereas immediate worsening of glycaemic control often occurs in those with pre-existing diabetes. Medium-acting corticosteroids mainly induce postprandial hyperglycaemia, with glycaemic peaks occurring 4–8 h after administration and a nocturnal low. Hence, monitoring of plasma fasting glucose alone, particularly before the

### Panel 2: Case vignette of checkpoint inhibitor-associated autoimmune diabetes (CIADM) after PDCD1 inhibitor use

#### Patient demographics and presentation

A 44-year-old woman with sigmoid colon cancer (pT4aN2bM0, stage III) initially underwent a loop transverse colostomy. She subsequently had disease progression with newly developed aortocaval nodal metastases, and was started on nivolumab therapy. She had no previous history of diabetes, and fasting glucose measurements during follow-up visits were within the normal range.

#### Medical history and laboratory findings

3 months after initiation of nivolumab, she developed progressive generalised weakness, accompanied by nausea, vomiting, and palpitations. Laboratory evaluation revealed severe hyperglycaemia and high anion gap metabolic acidosis with ketosis: a plasma glucose concentration of 31.0 mmol/L, a serum ketone concentration of 5.0 mmol/L, an arterial pH of 7.086, a PaCO<sub>2</sub> of 28.8 mmHg, and an HCO<sub>3</sub><sup>-</sup> concentration of 8.5 mmol/L. She was diagnosed with diabetic ketoacidosis. Antibody testing showed negative GADA (<0.59 IU/mL; reference <10 IU/mL) and negative IA-2A antibody (<0.95 U/mL; reference <7.5 U/mL). C-peptide concentrations were profoundly suppressed (fasting <0.01 ng/mL; 6-min stimulated <0.01 ng/mL), consistent with absolute insulin deficiency. These findings, combined with the temporal association with protracted nivolumab exposure, supported the diagnosis of CIADM.

#### Management and outcome

In this case, the patient developed abrupt onset of diabetes in the absence of previous diabetes history, presenting with fulminant insulin deficiency and diabetic ketoacidosis after 3 months of nivolumab therapy. The profoundly suppressed C-peptide concentration, negative autoantibodies, and the close temporal relationship to immune checkpoint inhibitor (ICI) exposure supported the diagnosis of CIADM rather than classic type 1 or type 2 diabetes. The patient was managed for diabetic ketoacidosis and discharged with insulin therapy.

#### Learning points

Early recognition of new-onset hyperglycaemia, especially when severe or accompanied by ketosis, is crucial. ICI-related diabetes frequently presents with diabetic ketoacidosis and requires lifelong insulin therapy. Increased awareness of this immunorelated adverse event enables timely diagnosis, appropriate management, and improved safety for patients undergoing immunotherapy.

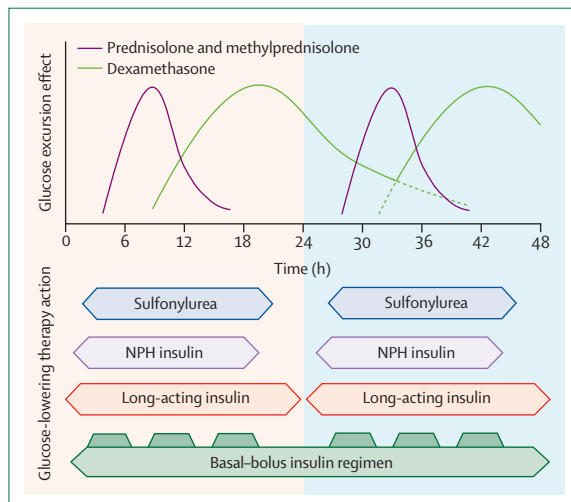
morning corticosteroid dose, is insufficient to detect corticosteroid-induced hyperglycaemia—monitoring of 2-h postprandial glucose is more appropriate.<sup>89,93</sup> Glucose-lowering treatments should be selected and timed to align with corticosteroid-induced glycaemic excursions, while minimising hypoglycaemia.<sup>89,94</sup> By contrast, long-acting corticosteroids, such as dexamethasone or multiple daily dosing schedules, generate prolonged hyperglycaemia (figure 3).

People at risk should undergo dysglycaemia screening (HbA<sub>1c</sub> and FPG concentrations, as well as 75 g oral glucose tolerance test) before corticosteroid initiation.<sup>66</sup> Given the heterogeneity of risk profiles and corticosteroid regimens, no universal treatment exists for corticosteroid-induced hyperglycaemia. For people receiving once-daily corticosteroids, oral glucose-lowering treatments can be considered, although their use is constrained by a limited dose titration, slow onset and protracted duration of action, and potential adverse

	Mechanism of action	Example of dosing regimens
Cytotoxic	Induction of apoptosis of malignant cells, especially lymphoid or lymphoplasmacytic in origin <sup>67,69-71,80,81</sup>	Diffuse large B-cell non-Hodgkin lymphoma: oral prednisolone 100 mg (or 40 mg/m <sup>2</sup> per day for 5 days, repeated every 21 days (R-CHOP regimen). Acute lymphoblastic leukaemia: pre-phase—oral prednisone 20–60 mg/day or oral or intravenous dexamethasone 6–16 mg/day for 5–7 days, given alone or in combination with another chemotherapy agent to assess chemosensitivity; induction phase: dexamethasone 40 mg daily (oral or intravenous) for 8 days in two 4-day blocks, for a total of 8 cycles (HyperCVAD regimen); maintenance phase: weekly doses of oral prednisolone or vincristine for 2–3 years. Multiple myeloma: oral dexamethasone 20–40 mg once weekly.
Anti-inflammatory and reversal of peritumoral oedema	Inhibits VEGF and inflammatory mediators, reducing vasogenic oedema and pressure in key systems, such as the brain and spinal cord <sup>73,82</sup>	Dexamethasone 4–16 mg/day (intravenous preferred in acute setting, can convert to oral once stable).
Management of immunotherapy-related adverse events	Downregulation of pro-inflammatory cytokines (IL-1, IL-6, TNF, IFN $\gamma$ ), inhibition of T-cell activation, suppression of macrophage and dendritic cell function, and suppression of autoimmune-like reaction triggered by immune checkpoint inhibitors; <sup>75</sup> treatment of ICANS or CRS in multiple myeloma <sup>81</sup>	Oral prednisolone 1–2 mg/kg per day or intravenous methylprednisolone 1–2 mg/kg per day; intravenous dexamethasone 20–80 mg/day (in four divided doses) or intravenous methylprednisolone 4 mg/kg per day.
Premedication for hypersensitivity prevention with immunotherapy	Suppression of cytokine-mediated inflammation and immune activation, often given together with anti-histamines to mitigate histamine-mediated reactions and antipyretics—commonly used before administration of taxane-based chemotherapies (eg, docetaxel, paclitaxel) or immunotherapies such as anti-CD20 (eg, rituximab, ofatumumab), anti-CD38 (eg, daratumumab) anti-CD52 (eg, alemtuzumab), and anti-CD19 or anti-CD3 (eg, blinatumomab) <sup>76</sup>	Dexamethasone 8–24 mg (pre-taxane or blinatumomab administration); methylprednisolone 1–2 mg/kg or 60–100 mg (for anti-CD52 and anti-CD38); oral prednisolone 20–100 mg (for anti-CD20).
Anti-emetic	Inhibition of prostaglandin synthesis, serotonin release from enterochromaffin cells, and direct and synergistic effect with 5HT-3 antagonists and neurokinin 1-receptor antagonists on nucleus tractus solitarius and area postrema <sup>77</sup>	Dexamethasone 8–20 mg (either oral or intravenous) before chemotherapy, and 4–8 mg/day for 1–3 days after chemotherapy.
Appetite stimulation and symptom palliation in advanced cancer	Hypothalamic modulation via enhancement of orexigenic signals, indirect improvement of anorexic effects from pro-inflammatory cytokines <sup>78,79</sup>	Oral dexamethasone 2–4 mg daily or oral prednisolone 10–20 mg daily or intravenous methylprednisolone 16 mg twice daily.

5HT-3=5-hydroxytryptamine 3. CRS=cytokine release syndrome. HyperCVAD=Hyper-fractionated cyclophosphamide, vincristine, adriamycin (or doxorubicin), and dexamethasone. ICAN=immune effector cell-associated neurotoxicity syndrome. IFN $\gamma$ =interferon gamma. R-CHOP=rituximab, cyclophosphamide, hydroxydaunorubicin (or doxorubicin), oncovin (or vincristine), and prednisone. TNF=tumor necrosis factor. VEGF=vascular endothelial growth factor.

**Table: Indications, mechanisms of action, and dosing regimens of corticosteroids in cancer care**



**Figure 3: Onset and duration of hyperglycaemia with different corticosteroids, and onset and duration of action of oral glucose-lowering treatments and insulin**  
 Time course of corticosteroid-induced hyperglycaemia and alignment of preferred glucose-lowering strategies. Prednisolone and methylprednisolone cause an onset of hyperglycaemia at 4 h, peaking at 6 h, and resolving by 12–16 h, best matched by sulfonylureas or NPH insulin. Dexamethasone produces hyperglycaemia with onset at 8–12 h, but with a protracted effect for up to 24–36 h. Long-acting or basal-bolus insulin regimens provide optimal coverage. NPH=neutral protamine hagedorn.

effects.<sup>91</sup> The action of meglitinides and short-acting sulfonylureas might best align with the glycaemic excursions associated with short-to-intermediate acting corticosteroids, although there can be a risk of delayed hypoglycaemia.<sup>89,91,94</sup> Metformin can mitigate longer-term complications of corticosteroids, but the benefit in acute hyperglycaemia is less evident.<sup>91,95</sup> DPP4 inhibitors are well tolerated, but provide modest glucose lowering.<sup>89,91</sup> GLP-1 receptor agonists are potent and have a low risk of hypoglycaemia, but their use can be limited by gastrointestinal adverse effects, particularly in people receiving emetogenic chemotherapy.<sup>89</sup> SGLT2 inhibitors increase the risks of genital tract infection<sup>96</sup> and osteoporosis,<sup>97</sup> exacerbating steroid-related adverse effects, and are generally ineffective for corticosteroid-induced hyperglycaemia.<sup>91,98</sup>

Insulin treatment is preferred for people receiving multiple daily corticosteroid doses or long-acting agents, or for those with pre-existing type 2 diabetes and a persistent glucose concentration of 10 mmol/L or more.<sup>91</sup> For once-daily regimens of intermediate-acting corticosteroids, such as prednisolone, morning co-administration with basal human insulin best aligns with the pattern of corticosteroid-induced hyperglycaemia.<sup>89,91</sup> In a randomised crossover trial involving people receiving cyclical corticosteroids for cancer

treatment, intermediate-acting insulin showed superior glycaemic control than sliding-scale insulin (mean absolute difference in time in range [3.9–10 mmol/L]: 13.5% [SD 19.1];  $p < 0.001$ ), without compromising safety.<sup>99</sup> In this trial, people received a median prednisolone-equivalent dose of 50 mg for 3 days per cycle, with intermediate-acting insulin titrated to bodyweight.<sup>99</sup> Long-acting basal insulin is appropriate for people treated with long-acting glucocorticoids, such as dexamethasone. Basal–bolus regimens offer the greatest efficacy and flexibility in people with severe or unstable hyperglycaemia (figure 3). Panel 3 describes a case vignette of the clinical challenges encountered in corticosteroid-induced diabetes.

### Somatostatin receptor ligand-induced hyperglycaemia

Functional NETs, particularly pituitary neuroendocrine tumours (PitNETs), such as acromegaly and Cushing's disease, are associated with hyperglycaemia through well established mechanisms.<sup>100,101</sup> Somatostatin receptor ligands (SSRLs), a cornerstone therapy for PitNETs, can also induce glycaemic perturbation. First-generation SSRLs (eg, octreotide and lanreotide) act primarily on somatostatin receptor 2 (SSTR2) and somatostatin receptor 5 (SSTR5). Their effects on glucose homeostasis are bidirectional: glycaemia can improve by suppression of growth hormone secretion and its downstream metabolic effects, but can also worsen due to direct pancreatic inhibition of insulin secretion. The net glycaemic effect differs and depends on the underlying susceptibility to fasting or postprandial hyperglycaemia.<sup>102</sup>

Pasireotide, a second-generation SSRL with high affinity for SSTR5, provides superior biochemical control in acromegaly. It is also effective for corticotroph tumours, which strongly express SSTR5. Its major limitation is marked hyperglycaemia driven by reduced insulin secretion, modest glucagon suppression, and attenuated incretin response.<sup>103</sup> The reported incidences of hyperglycaemia with pasireotide are higher in Cushing's disease (68.4–73.0%) than in acromegaly (57.3–67.0%).<sup>10</sup> By contrast, pegvisomant, a growth hormone receptor antagonist, lowers IGF-1 without suppressing insulin secretion, thereby improving insulin resistance and glycaemia in people with acromegaly, particularly in those with diabetes, although high doses are often required due to increased hepatic growth hormone receptor expression in hyperinsulinaemic states.<sup>104</sup> The challenges of managing SSRL-induced hyperglycaemia are described in the case vignette in panel 4.

Previous reports have suggested that cessation of pasireotide can reverse hyperglycaemia.<sup>105,106</sup> In people who are euglycaemic at baseline, the risk factors<sup>107</sup> for developing hyperglycaemia during pasireotide treatment are overweight and obesity (BMI >25 kg/m<sup>2</sup>), dyslipidaemia, an HbA<sub>1c</sub> of more than 5.3% (35 mmol/mol), or a 2-h plasma glucose concentration

of more than 9.0 mmol/L following a 75 g oral glucose tolerance test.<sup>108</sup> Metformin and incretin-based therapy are useful for managing SSRL-induced hyperglycaemia. In an open-label randomised controlled trial in patients with Cushing's disease or acromegaly treated with pasireotide, incretin-based therapy (sitagliptin followed by liraglutide) was associated with a numerically greater reduction in HbA<sub>1c</sub> than insulin (between-group difference –0.28%, 95% CI –0.63 to 0.08). In the same study, 46 of 249 patients (18.5%) had glycaemic control with oral glucose-lowering therapy alone, of whom 43 (93.5%) were managed with metformin monotherapy.<sup>109</sup> A management algorithm proposed by a group from Recordati Rare Diseases in Europe recommends: (1) initiating metformin in people with normoglycaemia who develop new-onset hyperglycaemia, (2) sequential addition of a GLP-1 receptor agonist or SGLT2 inhibitors in people with pre-existing diabetes, or (3) de novo initiation of a GLP-1 receptor agonist or SGLT2 inhibitors, tailored to the cardio–kidney–metabolic risk profile.<sup>110</sup>

### Panel 3: Case vignette of corticosteroid-induced diabetes

#### Patient demographics and presentation

An 18-year-old woman presented with a persistent 2-week history of fever and right lower limb pain. Initial imaging showed multiple musculoskeletal collections with diffuse lymphadenopathy, and laboratory tests showed persistent pancytopenia. Bone marrow aspiration and trephine biopsy substantiated a diagnosis of B-cell acute lymphoblastic leukaemia.

#### Medical history and treatment context

At diagnosis, the patient had underweight, with a BMI of 15.2 kg/m<sup>2</sup> and a baseline HbA<sub>1c</sub> of 5.8% (40 mmol/mol). During the induction phase of chemotherapy, she received high-dose corticosteroids consisting of prednisolone of up to 60 mg/m<sup>2</sup> per day for the first 3 days, followed by dexamethasone 6 mg/m<sup>2</sup> per day for 1 month. Routine glucose monitoring was not initially performed because she had no classic risk factors for diabetes.

#### Adverse event of hyperglycaemia

On day 14 of chemotherapy, she reported dizziness and sustained a fall in the ward. Capillary blood glucose was 33.2 mmol/L, ketone concentration was 2.1 mmol/L, and venous blood gas analysis showed no acidosis.

#### Management and outcome

She was started on intravenous insulin infusion, and ketonaemia promptly resolved within 3 h, although hyperglycaemia persisted between 17 mmol/L and 25 mmol/L over the next 24 h. She was transitioned to a subcutaneous basal–bolus insulin regimen, but in-patient glycaemic control remained challenging, with glucose concentrations consistently ranging from 11 mmol/L to 15 mmol/L over the following 72 h. Insulin was gradually titrated to 1.3 U/kg per day and, 5 days later, her plasma glucose concentration was 7.8–10 mmol/L. Following the completion of a 1-month course of dexamethasone, her blood glucose normalised within 3 days, allowing for cessation of insulin therapy.

#### Learning points

Although corticosteroid-induced diabetes is more common in older individuals, potent corticosteroids can induce diabetes in people without classic risk factors. Additionally, intensive glucose-lowering treatment might be needed for glycaemic control.

**Panel 4: Case vignette of somatostatin receptor ligand (SSRL)-induced hyperglycaemia****Patient demographics and presentation**

The patient is a woman diagnosed with Cushing's disease at the 25-years-old, who presented with headaches, early-onset hypertension, and classic dermatological manifestations of Cushing's syndrome. MRI of the brain revealed a pituitary macroadenoma, and biochemical testing confirmed autonomous ACTH-dependent hypercortisolism arising from the pituitary. Transsphenoidal resection of the tumour was done at diagnosis, which led to the resolution of her hypertension and other symptoms.

**Medical history and treatment context**

At the age of 28 years, she developed disease recurrence, which was initially treated with steroidogenesis inhibitors, followed by a transsphenoidal resection 2 years later. Postoperatively, she went into remission and required hydrocortisone replacement at physiological doses for 2 years.

**Clinical findings and management**

At the age of 33 years, she developed type 2 diabetes, with an HbA<sub>1c</sub> of 7.5% (59 mmol/mol), a fasting plasma glucose (FPG) concentration of 6.5 mmol/L, and a BMI of 23.8 kg/m<sup>2</sup> at diagnosis. This event heralded a third recurrence of her Cushing's disease, supported by unsuppressed cortisol concentrations and recurrence of a pituitary adenoma on MRI. A third transsphenoidal surgery was done, but did not result in remission. She was started on steroidogenesis inhibitors to control her hypercortisolism and subsequently underwent stereotactic radiosurgery.

While awaiting the effects of stereotactic radiosurgery, bridging therapy was done with pituitary-directed therapy with cabergoline (0.5 mg thrice weekly). Despite treatment, her disease remained active, with persistently elevated urinary cortisol concentrations. Subsequently, pasireotide (0.6 mg twice daily) was initiated, at which point her baseline HbA<sub>1c</sub> was 7.4% (57 mmol/mol) and her FPG concentration was 9 mmol/L (while on metformin 850 mg twice daily).

**Adverse events and onset of worsening hyperglycaemia**

Within 1 week of starting pasireotide, her self-reported fasting and pre-meal capillary glucose concentrations increased to 18–20 mmol/L. Basal-bolus insulin therapy was initiated for glycaemic control. Her HbA<sub>1c</sub> increased to 9.8% (84 mmol/mol) at 3 months, and 10.1% (87 mmol/mol) at 6 months on pasireotide. Her 24-h urinary cortisol concentrations and blood pressure normalised and her features of Cushing's disease (facial puffiness, retrocervical fat pad) resolved, but her weight remained the same.

Pasireotide was stopped 9 months later due to intolerable adverse effects, including nausea and bloating. She was then switched to cabergoline, and her 24-h urine cortisol remained within the normal range, indicating adequate biochemical control. 1 month after stopping pasireotide, her HbA<sub>1c</sub> improved to 8.5% (69 mmol/mol) and her diabetes treatment was de-escalated to a regimen of bedtime insulin with a daytime sulfonylurea regimen. At the time of writing, 8 years later (and 19 years after her initial diagnosis of Cushing's disease), her condition remains under control based on biochemical and other clinical parameters. However, her diabetes progressed and required treatment intensification to basal-bolus insulin and a GLP-1 receptor agonist to optimise glycaemic control.

**Learning points**

Hyperglycaemia can develop rapidly after initiation of SSRL, such as pasireotide, and often remains elevated due to its mechanism of action. Close monitoring for worsening dysglycaemia and appropriate initiation or escalation of insulin therapy is required in these patients. Given the impact of SSRLs on glycaemic control, glycaemic measures are unreliable indicators of primary disease response in Cushing's disease. Other clinical parameters, such as hypertension, dermatological, musculoskeletal manifestations, and biochemical assessment of cortisol secretion, are required for appropriate monitoring of primary tumour activity.

**New-onset diabetes as an early manifestation of cancer**

New-onset diabetes in adults, particularly in the absence of conventional metabolic risk factors, can indicate an underlying malignancy rather than classic type 2 diabetes. Pancreatic cancer is the malignancy most commonly associated with this presentation. Up to 50% of people with newly diagnosed pancreatic cancer have diabetes at the time of diagnosis.<sup>7</sup> Approximately 1% of people aged 50 years or more with diabetes will go on to be diagnosed with pancreatic cancer within 3 years.<sup>111</sup> Compared with other periampullary or pancreatic cancers, pancreatic ductal adenocarcinoma is the most common location.<sup>112</sup>

People with pancreatic ductal adenocarcinoma have a higher background incidence of diabetes than age-matched and sex-matched controls for as long as

15 years before cancer diagnosis (adjusted hazard ratio [HR] 3.83, 95% CI 3.68–3.98), with the strongest association observed within 1 year of cancer diagnosis (adjusted HR 9.07, 95% CI 8.33–9.87).<sup>113</sup> This risk increases markedly with advancing age—ie, beyond 50 years.<sup>113</sup> Similarly, pre-cancerous lesions, such as intraductal papillary mucinous neoplasms, are increasingly recognised as being associated with glucose dysregulation. Impaired glucose tolerance or new-onset diabetes in people with intraductal papillary mucinous neoplasms can signal malignant transformation or progression.<sup>114</sup> Diabetes is present in 17.7% of people with intraductal papillary mucinous neoplasms, increasing to 31.7% in those with malignant lesions. Compared with those who do not have diabetes, people with diabetes have a 2–4 fold higher risk of malignant progression.<sup>114</sup>

The relationship between diabetes and pancreatic cancer is complex. Long-standing type 2 diabetes and chronic pancreatitis are established risk factors for incident pancreatic ductal adenocarcinoma, whereas new-onset diabetes within 3 years of cancer diagnosis is increasingly recognised as a paraneoplastic occurrence. Proposed mechanisms of paraneoplastic diabetes include tumour-derived factors, such as adrenomedullin, islet amyloid polypeptide, inflammatory cytokines, fibroblast growth factor-4, and sulfhydryl-oxidase 2, which impair both insulin action and secretion. Remission of diabetes after tumour resection with preservation of pancreatic tissue further supports this mechanistic link.

In advanced disease, extensive pancreatic tissue destruction or the need for sub-total or total pancreatectomy leads to type 3c pancreatogenic diabetes. This form of diabetes is distinct from type 1 and type 2 diabetes in that absolute insulin deficiency from  $\beta$ -cell loss coexists with impaired glucagon secretion from  $\alpha$ -cell loss, and is often accompanied by exocrine pancreatic insufficiency, malabsorption, and attenuated incretin response.<sup>115</sup> Clinically, patients can present with brittle diabetes, characterised by glycaemic lability, frequent hypoglycaemia secondary to  $\alpha$ -cell loss, and concurrent nutritional deficiencies.<sup>115</sup> Metformin might be used initially if tolerated, but insulin is often required early, and careful titration is essential given diminished counter-regulatory glucagon. Real-time CGM can improve glycaemic control in this population, as shown in a 2025 trial of chronic pancreatitis-associated type 3c diabetes.<sup>116</sup> Compared with self-monitoring of blood glucose, CGM improved the time in range (3.9–10.0 mmol/L) by 7.46% (95% CI 1.67–13.25), reduced the time above range (>10 mmol/L) by 6.55% (95% CI 2.59–10.51), and reduced the time below range (<3.9 mmol/L) by 0.91% (95% CI 0.03–1.79) over 50 days, with a numerical reduction in level 2 hypoglycaemia. Notably, the presentation of new-onset diabetes is heterogeneous and does not necessarily correspond with the stage and severity of pancreatic cancer. Panel 5 describes a case vignette of diabetes as a metabolic manifestation of pancreatic adenocarcinoma.

Risk stratification tools have been developed to identify people with new-onset diabetes at the highest risk for pancreatic cancer. The most notable is the Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) score, which incorporates age at onset of diabetes, weight loss, and changes in glycaemic control.<sup>117</sup> In the derivation cohort, an ENDPAC score of 3 or more identified pancreatic cancer with 80% sensitivity, 80% specificity, and an area under receiver operating characteristic curve (AUC) of 0.87. In external validation, performance was similar (78% sensitivity, 82% specificity), with enrichment of pancreatic cancer prevalence from 0.82% to 3.6% (ie, a 4.4-fold increase).<sup>117</sup>

### Panel 5: Case vignette of diabetes as an early manifestation of cancer

#### Patient demographics and presentation

A 78-year-old man presented with a history of progressive abdominal fullness, severe postprandial pain, and an unintentional 10 kg weight loss over 2 months.

#### Medical history and treatment context

He had a history of hypertension and benign prostatic hyperplasia, but otherwise no previous diagnosis of diabetes and no recent documentation of dysglycaemia.

#### Clinical and laboratory findings

Imaging revealed a 5.7 cm pancreatic mass involving the head and body of the pancreas, with encasement of the coeliac, splenic, and common hepatic arteries. Biopsy confirmed pancreatic adenocarcinoma (cT4N1M0, stage III). During evaluation, severe hyperglycaemia was noted, with a fasting plasma glucose concentration of 15.1 mmol/L and an HbA<sub>1c</sub> of 11.9% (107 mmol/mol), consistent with new-onset diabetes.

#### Management and outcome

He underwent duodenal stenting for gastric outlet obstruction and a subcutaneous venous access port implantation in preparation for systemic therapy. Initially, only insulin therapy was commenced. Subsequently, his plasma glucose concentrations remained well controlled, with low dose insulin (6–8 units), suggesting partially preserved endogenous insulin secretory function. He was subsequently transitioned to a combination of metformin and linagliptin.

#### Learning points

New-onset diabetes or rapidly worsening glycaemic control in older adults might represent a paraneoplastic presentation of pancreatic cancer.

### Panel 6: Key take-home messages

- The bidirectional association between diabetes and cancer, amplified by obesity and other cardiometabolic conditions, necessitates close vigilance across specialties for the diabetogenic effects of anti-cancer treatments.
- The multisystemic nature of glucose metabolism, multicausality of diabetes, and multitargeted effects of anti-cancer treatments necessitate structured clinical evaluation of people presenting with diabetes.
- People with atypical features, stable diabetes with sudden glycaemic deterioration, and advanced age, with acute onset of diabetes and substantial weight loss, warrant further evaluation.
- All people starting potentially diabetogenic anti-cancer therapies should at least undergo baseline glycaemic evaluation with fasting plasma glucose and HbA<sub>1c</sub>. A 75 g oral glucose tolerance test can be selectively considered, balancing additional cost and care burden against incremental diagnostic yield, especially among those taking agents that exacerbate insulin resistance (PI3K-AKT-mTOR inhibitors, antibody-drug conjugates, corticosteroids, and somatostatin receptor ligands), those with additional diabetes risk factors or borderline dysglycaemia, or those in whom HbA<sub>1c</sub> might be unsuitable. Intensification of glycaemic control is required in people with pre-diabetes or known diabetes; however, even among those who are normoglycaemic at baseline, regular glucose monitoring is necessary to detect incident hyperglycaemia.
- All people undergoing anti-cancer treatments should be informed about potential adverse effects, symptoms of hyperglycaemia, diabetic ketoacidosis, or hyperosmolar hyperglycaemic syndrome, and educated about appropriate self-monitoring of blood glucose to detect acute metabolic decompensation.
- Understanding glucose metabolism and the mechanisms of glucose-lowering and anti-cancer treatments, together with structured clinical evaluation and disease registers, is key to advancing prevention and management of diabetes-cancer comorbidity.

### Search strategy and selection criteria

We structured the search into concept clusters of secondary diabetes and interactions with specific oncology and neuroendocrine tumour treatments, followed by new-onset diabetes as a manifestation of cancer. We searched PubMed, MEDLINE, and Google Scholar for articles from database inception to Sept 30, 2025. The terms we used were: secondary diabetes ("secondary diabetes" OR "drug-induced diabetes" OR "hyperglycaemia") AND cancer therapy ("cancer therapy" OR "cancer treatment" OR "oncology" OR "PI3K inhibitor" OR "mTOR inhibitor" OR "AKT inhibitor" OR "antibody-drug conjugate" OR "immunotherapy" OR "immune checkpoint inhibitors" OR "immune-related adverse events" OR "glucocorticoids" OR "corticosteroids"). For neuroendocrine tumour treatment-induced dysglycaemia, we used "diabetes" OR "hyperglycaemia" OR "dysglycaemia" AND "somatostatin receptor ligands" OR "somatostatin receptor analogues". For new-onset diabetes as a manifestation of cancer presentation, we used "secondary diabetes" OR "hyperglycaemia" OR "dysglycaemia" AND "paraneoplastic" OR "cancer" OR "pancreatic cancer". We further screened the reference lists of key articles to identify additional relevant studies. We also referred to major oncology and diabetes guidelines. We only included English-language, peer-reviewed articles, systematic reviews, original research, and guidelines. We excluded conference abstracts, preprints without peer review, and supplements. We incorporated case vignettes from the authors' clinical experiences relevant to each subtopic to contextualise the discussion.

However, preliminary prospective data from the PANDOME study show that, although ENDPAC effectively enriches risk, it is insufficient as a standalone trigger for imaging. In 109 participants, with many meeting the high-risk threshold ( $\geq 3$  in 35.6% of those with new-onset diabetes and  $\geq 5$  in 75% of those with rapidly worsening diabetes), only one case (0.9% of participants) of pancreatic cancer was detected, occurring in an older participant with an ENDPAC score of 11.<sup>118</sup> These findings suggest that ENDPAC is most informative when interpreted alongside clinical deterioration, such as rapid worsening of HbA<sub>1c</sub> concentrations, unintentional weight loss, or a new insulin requirement.<sup>118</sup> Additional early-stage efforts include predictive models with volatile organic compound profiling from point-of-care breath tests, which might complement future risk stratification strategies.<sup>118,119</sup>

Beyond pancreatic cancer, new-onset diabetes has been associated with other malignancies through various paraneoplastic mechanisms. Hepatocellular carcinoma has been linked to hepatogenous diabetes, characterised by hepatic insulin resistance and impaired insulin clearance.<sup>120</sup> Lung cancers, particularly small-cell variants, can produce ectopic adrenocorticotrophic hormones, leading to Cushing's syndrome and secondary diabetes.

Rarely, NETs such as glucagonomas and pheochromocytomas induce diabetes by excess secretion of counter-regulatory hormones. Taken together, these observations highlight the importance of considering occult malignancy in people with either unexplained or atypical new-onset diabetes, particularly when accompanied by constitutional symptoms.

### Conclusion and future perspectives

This Review highlights advances in onco-endocrinology, while also underscoring knowledge gaps across all domains discussed. The multiple organs and pathways implicated in glucose homeostasis are also highlighted by the so-called off-target effects of anti-cancer treatment. Understanding these pathways and the risk factors for diabetes will help providers anticipate the risk of drug-induced or drug-worsened hyperglycaemia and its management.

We summarise the key take-home messages in panel 6. Although drug-specific guidelines are emerging, whether recommendations developed for one treatment can be extrapolated to others within the same class remains uncertain—for example, whether guidance for PI3K inhibitors is applicable to pan-PI3K inhibitors. The compounded diabetes risk posed by multimodality treatment, such as combined ICI and corticosteroids, needs to be clearly defined. Even for established treatments such as corticosteroids, the optimal role of contemporary technologies—for example, CGM—has not been fully established.

Real-world data, including clinical registers of novel cancer treatments, are essential for characterising the incidence, severity, and consequences of treatment-associated hyperglycaemia. Mapping disease trajectories will help identify the optimal windows for intervention to prevent acute and long-term complications. Importantly, it is key to understand when preventive approaches are necessary, particularly in high-risk populations, such as those with pre-existing diabetes or those requiring multimodality treatment. Pre-emptive glucose-lowering treatment, such as prophylactic metformin for people receiving PI3K inhibitors, has been proposed, but high-quality evidence is needed before such approaches can be adopted in routine care.

Efforts should also focus on evaluating novel monitoring and treatment approaches, including continuous glucose or ketone monitoring systems and telemedicine-supported home surveillance systems. A person-centred approach is needed to ensure timely access to clinical care when metabolic complications arise. Although many challenges remain, endocrinologists, oncologists, internists, and other health-care professionals must work together in a multidisciplinary working environment to address the diabetes burden.

#### Contributors

L-LL and JCNC conceived the idea and general plan of this Review. NK-YH and Q-HL contributed equally to the writing of the first draft,

tables, and figures. Y-GO produced the final versions of the figures. EIE, H-YL, SRV, and I-WY contributed to the case vignettes. All authors contributed to the draft outline of topics covered, critically reviewed the final draft of the manuscript for important intellectual content, and agreed to be accountable for all aspects of the manuscript. L-LL and JCNC finalised the manuscript. All authors approved the final manuscript for publication.

#### Declaration of interests

NK-YH has received speaker honoraria from AstraZeneca, Amgen, Novo Nordisk, and Zuellig Pharma; travel grants for conferences from Amgen and Zuellig Pharma; and a research grant from AstraZeneca. Q-HL has received speaker honoraria from AstraZeneca, Novo Nordisk, and Zuellig Pharma; travel grants for conferences from Novo Nordisk, Zuellig Pharma, and Viartis; and a research grant from Novo Nordisk for an industry-sponsored trial. KK has acted as a consultant, speaker, or received grants for investigator-initiated studies for AstraZeneca, Bayer, Novo Nordisk, Sanofi, Servier, Lilly, Merck Sharp and Dohme, Boehringer Ingelheim, Oramed Pharmaceuticals, Pfizer, Roche, Daiichi Sankyo, Applied Therapeutics, Embecta, and Nestlé Health Science. MS has received research grants and speaker and advisory board honoraria from Astellas, AstraZeneca, Bicycle Therapeutics, Bristol Myers Squibb, Eisai, Ferring, Ipsen, Johnson & Johnson, Merck, and Merck Sharp and Dohme; and travel grants from Ipsen, Merck, and Merck Sharp and Dohme. EIE has received research grants and speaker honoraria via her institution from Abbott, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Lilly, Endogenex, New Amsterdam Pharma, Novartis, Novo Nordisk, and Omnipod. JCNC reported receiving research grants through her affiliated institutions and speaker honoraria from Abbott, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Celltrion, Hua Medicine, Powder Pharmaceuticals, Lilly, Merck Sharp and Dohme, Merck Serono, Pfizer, Roche, Sanofi, Servier, Viartis, and Zuellig Pharma. JCNC holds patents awarded to the Chinese University of Hong Kong for using genetic markers to predict diabetes and its complications for personalised care. JCNC is a cofounder of a biotechnology start-up company, GemVCare, with partial support from the Hong Kong Government Innovation and Technology Commission for providing precision diabetes care, and is chief executive officer (pro bono) of the Asia Diabetes Foundation, which developed the JADE Platform®. L-LL has received research grants via her institution from Abbott Diabetes Care, AstraZeneca, and Novartis; speaker honoraria from Abbott, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Roche Diabetes Care, and Zuellig Pharma. All other authors declare no competing interests.

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